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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/852,020 05/06/97 MARUYAMA

HM12/0717
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EXAMINER

LEFFERS JR. G	
ART UNIT	PAPER NUMBER

1636
DATE MAILED:

07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/852,020

Applicant(s)

MARUYAMA ET AL.

Examiner

Gerald Leffers

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 57-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 57-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

ZETA ADAMS
PATENT ANALYST

Zeta Adams

DETAILED ACTION

Receipt is acknowledged of applicants' request for a Continued Prosecution Application, filed 7/5/01 as Paper No. 28, in which applicants' requested the amendment filed 1/18/01 (Paper No. 22) be entered. Accordingly, claim 57 has been amended as specified. No other new changes to the claims were specified in either paper. No new arguments have been presented in Paper No. 28 against rejection of claims 57-60 under 35 U.S.C. 112, first paragraph, for reasons of record in Paper No. 20. As the same grounds of rejection stand for reasons of record in Paper No. 20, this action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 57-60 encompass recombinant lambdoid bacteriophage vectors or bacteriophage having a cistron comprising the coding sequence for an anchor matrix gene operatively linked to coding sequences for a linker polypeptide and a desired, preselected polypeptide such that expression of the recombinant cistron during morphogenesis results in incorporation and display

of the recombinant fusion polypeptide comprising the desired polypeptide sequence on the surface of the mature lambdoid phage particle. The claims encompass any of the potential anchor matrix polypeptides (e.g. head proteins: pE, pD, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), or portions thereof, as the matrix anchor component of the fusion polypeptide that is displayed on the surface of the phage particle. Each of these polypeptides has its own unique structure and plays a unique role in phage morphogenesis, having a distinct set of temporal and spatial interactions with other phage proteins during the assembly of the mature phage particle. Thus, the instant claims are very broad genus claims directed to a number of distinct structural polypeptides having different structural and functional characteristics.

While the specification has described adequately one subset of the claimed genus, those embodiments drawn to the tail polypeptide pV, there is only the broadest description of any of the remaining members of the genus. The claims and specification only describe a conditionally expressible cistron encoding an anchor matrix polypeptide operatively linked to a linker polypeptide coding sequence which is in turn linked to the coding sequence for a desired, preselected polypeptide. There is no description of where within the coding sequence for any of the other members of the genus of potential anchor matrix polypeptides one would insert the sequences for the linker polypeptide and the desired polypeptide. There is no description in the prior art or within the specification as to which portions of any of the other anchor matrix polypeptides might be dispensable for morphogenesis and thus potentially suitable for insertion of foreign sequences. There are no relevant examples in the specification as filed of such a fusion construct for any of the potential anchor matrix polypeptides other than for pV. Because

of the unique sequences, structural features and functions for each of the other anchor matrix proteins, one of skill in the art can not extrapolate from the description of fusion constructs comprising pV what would be a permissible insertion and fusion for any of the other anchor matrix proteins such that a recombinant polypeptide expressed from such a construct would be assembled and displayed on the surface of the mature phage particle. Thus, it would not be possible for the skilled artisan to envision a representative number of the remaining members of the broadly claimed genus of recombinant anchor-matrix fusion proteins. Therefore, there is not sufficient description in the specification to inform a skilled artisan that the applicant was in possession of the full, large breadth scope embraced by the claimed invention: a recombinant lambdoid bacteriophage vector or bacteriophage comprising a cistron encoding an anchor matrix polypeptide other than pV operatively linked to the coding sequence for a linker polypeptide and desired, preselected polypeptide for display of the recombinant fusion protein on the surface of the mature phage.

Claims 57-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant lambdoid bacteriophage vector or bacteriophage comprising fusions with lambdoid bacteriophage tail polypeptides that are pV, does not reasonably provide enablement for embodiments wherein the lambdoid phage anchor matrix protein is other than pV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving a recombinant lambdoid bacteriophage which displays on the surface of the bacteriophage a fusion protein including one of the anchor matrix proteins operatively linked in the direction of the amino terminus to the carboxy terminus to a linker polypeptide and a polypeptide of choice. This invention further involves complex issues of which phage matrix polypeptides are suitable for forming such fusion proteins both in terms of accessible display on the outer surface of the phage and in the ability of the phage to assemble properly once the fusion protein is expressed during morphogenesis. Once a suitable matrix polypeptide has been identified, there are still complex issues as to where to insert the linker and preselected polypeptide into the desired matrix polypeptide such that assembly is not impaired and accessible display is maintained. Issues of what size and type of polypeptide will be tolerated and displayed in an accessible manner for each desired polypeptide are also present for the instant claims.

Breadth of the claims: The breadth of the claims, encompassing any of the proteins displayed on the surface of the phage particle (e.g. head proteins: pE, pD, pW, pFII, pB*, pX1, pX2; tail proteins: pV, pJ, pG, pM and pT; page 22 lines 13-21), greatly increases the complexity of the invention with regard to how each potential matrix anchor protein is assembled into the phage, the role each potential matrix anchor protein plays in morphogenesis and assembly (i.e. is

it dispensable for proper assembly and function?) and where within the coding region for the potential matrix anchor protein to insert the coding sequences for the polypeptide linker and preselected polypeptide in order to express a fusion protein that will allow its incorporation into the phage capsid in such a way as to allow morphogenesis and accessible display of the preselected protein on the mature phage particle.

Guidance of the specification/The existence of working examples: The specification provides specific guidance and working examples only for the major tail protein pV and the prior art is silent on fusion proteins that include the other tail proteins or head proteins of lambdoid phage. Reference to the other outer-surface proteins of the phage particle is only suggestive that they are suitable for use in the invention by virtue of their location on the surface of the phage tail and capsid. There is no guidance within the specification as filed regarding which portions of the other potential matrix anchor proteins are dispensable for assembly and which may present suitable locations for insertion of heterologous sequences. There is no guidance within the specification as filed as to which particular nucleotide sequences within the gene encoding any potential matrix anchor protein, other than pV, is suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such a construct will not disrupt particle assembly and will allow functional, accessible display of the desired preselected polypeptide on the mature phage particle.

State of the art: The state of the art at the time of applicants' invention was high, requiring a high degree of skill in order to make and use the claimed invention. In fact, there is no guidance in the prior art regarding which portions of the potential matrix anchor proteins are dispensable for assembly and which may present suitable locations for insertion of heterologous

sequences. There is no guidance within the prior art as to which particular nucleotide sequences within the gene encoding any potential matrix anchor protein are suitable for insertion of a heterologous coding sequence such that the expressed fusion protein from such a construct will not disrupt particle assembly and will allow functional, accessible display of the desired preselected polypeptide on the mature phage particle.

Predictability of the art: The art of displaying a desired polypeptide in an accessible manner on a phage particle is not predictable, as evidenced by applicants' own teachings. The specification discloses that the pV is present in 180-200 copies in the mature tail. The specification teaches (page 115, 1st paragraph) that addition of a linker polypeptide appears to interfere with tail assemble, since the plaques were smaller in su^+ hosts. Further, at page 126 of the specification it is disclosed that phage tails displaying beta-galactosidase contained only one to a few copies of the fusion polypeptide even though higher levels of incorporation could have been expected, indicating the fusion polypeptide interferes with some aspect of tail assembly or infection. Therefore, successful incorporation into a mature tail of pV protein fusions is somewhat unpredictable.

Each of the matrix proteins occupies a unique position in the mature particle, and performs a unique role during particle assembly. The successful incorporation into the tail of altered forms of one of the tail proteins (e.g. pV) does not provide evidence that any of the other matrix proteins (head or tail proteins) can be similarly modified without impairing their unique role in phage assembly. With respect to the pV protein, it was known in the prior art that this protein comprised a "knob" that extended out from the surface of the phage that was dispensable. It is this "knob" that is replaced by the displayed peptide in the disclosed invention.

Replacement of this "knob" with a heterologous peptide sequence would not have been expected *a priori* to interfere with phage assembly. However, as disclosed in the instant specification it was necessary to replace the knob with the desired peptide in only a limited number of recombinant pV subunits in the phage tail, or assembly was impaired. It is for this reason that Ladner is not deemed to be prior art for the prophetic disclosure of using pV peptide fusions to display proteins. No comparable dispensable peptide sequence is disclosed in either the specification or prior art that one could have expected could be replaced with a desired peptide, without interfering with phage assembly. As recited in the claims, the fusion polypeptide comprises, from amino to carboxy terminus, a matrix anchor polypeptide, a linker polypeptide and a preselected polypeptide. Such an arrangement would therefore require that the carboxy terminus of a given matrix anchor protein be exposed on the surface of the particle and that the addition of other polypeptides to the carboxy terminus of the matrix anchor polypeptide not interfere with either expression of the matrix anchor gene or assembly of the matrix anchor/preselected polypeptide fusion into the phage.

Applicants have submitted Mikawa et al (Exhibit 1, Paper No. 8) as evidence of enablement for other capsid or tail proteins. However, Mikawa et al is not prior art and it is not clear that the methods used to obtain phage displaying polypeptides as pD fusions are commensurate with the teachings of the instant disclosure. For example, amino terminal fusions were made between the second and third codons, rather than at or after the initial codon (page 22, column 1). It is also noted that the primary author, Y.G. Mikawa, is not a named inventor on the instant application, which suggests that the contribution of Y.G. Mikawa is in addition to the instant disclosure. With regard to the predictability of making fusions comprising pD as the

matrix anchor portion of the fusion polypeptide, it is of note that the reference states in the first paragraph of the discussion (page 27) that the ends of pD are not involved in the interaction between pD subunits or between pD and pE subunits, "...an important result for which no guarantee existed at the start of this work.". As indicated above, there is no teaching or working example in the instant specification that indicates where in the pD coding sequence (or in the coding sequence of any of the other potential matrix anchor proteins) it is appropriate to insert coding sequences for the linker polypeptide and the preselected protein such that interaction among capsid components is not interrupted, that phage assembly is not impaired and the desired fusion protein is displayed in a functional, accessible manner. Also, as with pV, one cannot extrapolate from pD fusions where to make fusions to other capsid proteins, such that phage assembly is not impaired. Mikawa et al specifically states that the authors chose pD because it was dispensable provided the genome was less than 82% of wild type in length, a feature not true for the other capsid proteins.

The amount of experimentation necessary: Given the complex nature of the invention in which a fusion polypeptide comprising an anchor motif from the bacteriophage matrix is expressed during phage morphogenesis such that the fusion polypeptide is incorporated into the phage structure and displayed in an accessible and/or functional manner, the breadth of the claims which encompass any of the potential matrix anchor polypeptides displayed on the surface of the phage particle, the lack of guidance from the specification or the prior art as to which portions of any of the other potential matrix anchor proteins are dispensable for phage assembly or which would be appropriate for insertion of the coding sequences for the polypeptide linker and preselected polypeptide (even for pD) and the unpredictability of whether

a particular fusion will be incorporated into the phage particle in a fashion that does not disrupt subunit-subunit interaction and will allow accessible and/or functional display of the desired, preselected polypeptide on the mature particle, it would require undue, unpredictable experimentation to make even one embodiment of the claimed invention not involving pV as the matrix anchor protein. One would first have to envision an appropriate matrix anchor protein construct in which the coding sequence for the matrix anchor protein is operatively linked at a particular sequence with the coding sequences for a linker polypeptide and desired, preselected polypeptide, make the construct and express the hybrid gene during morphogenesis such that the fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle assembly and the unpredictability of the art as evidenced by applicants' own teaching regarding pV, it would then be necessary for one of skill in the art to envision a modification of the first matrix anchor/fusion protein construct, or an entirely different construct, which might be suitable for display of a desired protein on the surface of the phage particle, make the construct and express the hybrid gene during morphogenesis such that the second fusion protein might be incorporated into the phage particle and then determine whether functional phage particles are formed which display the desired, preselected polypeptide sequence in an accessible and/or functional manner. If again unsuccessful, which is likely given the lack of guidance from the specification or the prior art as to which portions of the other potential matrix anchor proteins are dispensable for particle

assembly and the unpredictable nature of the art as evidenced by applicants' own teachings regarding pV, it would be necessary for one of skill in the art to repeat the entire process until such time, if any, that a construct was identified which allows the expression of a fusion protein comprising one of the potential matrix anchor proteins with a desired, preselected polypeptide such that the fusion protein is successfully incorporated into the mature phage particle and the preselected polypeptide displayed in an accessible and/or functional manner. Such experimentation is undue, unpredictable experimentation and would be required in order to make and use any embodiment of the instant invention not comprising pV as the matrix anchor portion of the fusion protein, even the pD fusions of Mikawa et al, in light of the instant specification. Thus, applicants' claimed invention of a recombinant lambdoid bacteriophage vector or bacteriophage encoding protein fusions derived from any matrix anchor protein located on the surface of the phage particle operatively linked to a polypeptide linker and preselected polypeptide, is not considered to be fully enabled by the specification. Only in the case where the matrix anchor protein is derived from the pV polypeptide, as described in the specification, would there be a reasonable expectation of success in constructing a vector or bacteriophage which encodes a fusion polypeptide comprising the desired, preselected polypeptide expressed and displayed in an accessible and/or functional manner.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Rob Schwartzman, Ph.D., can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

DAVID GUZO
PRIMARY EXAMINER



GLJ
G. Leffers Jr., Ph.D.
Patent Examiner
Art Unit 1636
13 July 2001